REMARKS

The Claim Amendments

Applicants note that in the previous Amendment, claim 288 was incorrectly and inadvertently mis-numbered as "289" when in fact it should have been numbered "288." The claim numbering is corrected in the present Amendment.

Claims 296-386 stand canceled in the present amendment pursuant to the Restriction Requirement and without prejudice to the prosecution of their subject matter in related divisional, continuation, and continuation-in-part applications.

Claims 272, 273, 281, 284, 288, and 291 stand amended in the present Amendment.

Support for the amendments to claims 272, 273, 281, 288, and 291 is found, for example, in the claims as originally filed; at page 5, line 25; at pages 7-8, particularly page 7, lines 31-38 and page 8, lines 1-5; at pages 48-49, particularly at page 48, lines 16-33; page 79, line 1; and elsewhere in the specification and claims as originally filed. Typographical errors are corrected in claim 284.

No new matter is added by way of the claim amendments.

Applicants note that, pursuant to the Restriction Requirement mailed on October 14, 2009, the pending claims are drawn to a method of identifying a phenotype associated with a disruption of the gene which encodes for a native sequence PR0224 polypeptide, with the genus "eye abnormality," where the elected species is "retinal abnormality."

Priority

Applicants note that the USPTO acknowledges priority of the present application to U.S. Provisional Patent Application 60/530,043 filed on December 16, 2003.

The Claim Objections and Rejections

Claim 273 stands objected to as allegedly being drawn to a non-elected invention.

Claims 272, 273, 280, 282-284, and 291 stand rejected under 35 U.S.C. § 112, second paragraph as allegedly being incomplete for omitting essential steps.

Claims 272, 273, 280, 282-284, and 291 stand rejected under 35 U.S.C. § 112, first paragraph as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 272, 273, 280, 282-284, and 291 stand rejected under 35 U.S.C. § 112, first paragraph as allegedly failing to comply with the enablement requirement, the USPTO suggesting that the claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicants respectfully traverse the objection and these rejections.

The Objection to Claim 273

Claim 273 stands objected to as allegedly being directed to non-elected subject matter. However, Applicants note that, as amended, Claim 273 is directed to methods wherein the phenotype associated with the gene disruption comprises an eye abnormality, and is not directed to non-elected subject matter. Accordingly, Applicants submit that the objection of claim 273 is overcome.

The Rejections under 35 U.S.C. § 112, second paragaph

Claims 272, 273, 280, 282-284, and 291 stand rejected under 35 U.S.C. § 112, second paragraph as allegedly being incomplete for omitting essential steps. In particular, the USPTO suggests that Claim 272 does not recite any specific phenotype, and suggests that step (e) fails to relate back to the preamble.

However, Applicants note that Claim 272, as amended, provides that the phenotype associated with a disruption of the gene which encodes for a native sequence PRO224 polypeptide is an eye abnormality. Applicants further note that Claim 272, as amended, relates back to the preamble, providing that "whereby an agent which is determined to modulate an eye abnormality associated with a disruption of the gene that encodes for a native sequence PR0224 polypeptide is identified." Thus, Claim 272 is believed to be definite under 35 U.S.C. § 112, second paragraph, and its dependent claims 273, 280, 282-284, and 291 are believed to be definite under 35 U.S.C. § 112, second paragraph.

Accordingly, Applicants submit that the rejections of claims 272, 273, 280, 282-284, and 291 under 35 U.S.C. § 112, second paragraph are overcome.

The Rejections under 35 U.S.C. § 112, first paragraph (possession)

Claims 272, 273, 280, 282-284, and 291 stand rejected under 35 U.S.C. § 112, first paragraph as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In particular, the USPTO suggests that not all nucleotide sequences "that encode all PRO224, variants, and fragments thereof encompassed within the genus of a gene which encodes for a PRO224 polypeptide" have been disclosed.

Applicants traverse this rejection for at least the reason that Claims 272, 273, 280, 282-284, and 291 are directed to methods which recite the gene that encodes for a native sequence PR0224 polypeptide. Applicants disclose the nucleic acid and amino acid sequence of full-length native sequence PRO224 (see, e.g., Figures 1 and 2, SEQ ID NOs: 1 and 2). Applicants further disclose methods of isolating DNA (see, e.g., pages 106-107, and 112); methods utilizing non-human homologs of PRO224 (page 116, line 21 to page 117, line 27); and experimental methods and results preparing and using human PRO224 (page 146, line 7 to page 147 line 11) and PRO224 knock-out mice (page 162, line 18 to page 164, line 20). Thus, Applicants disclose sequences and methods used with human and mouse, and which are useful for other animals as well.

Thus, since the claim is directed to the gene which encodes for a native sequence PRO224 polypeptide, and since the objections are directed to an alleged lack of written description for nucleotide sequences that encode all PRO224, variants, and fragments thereof encompassed within the genus of a gene which encodes for a PRO224 polypeptide, Applicants submit that the rejection is overcome.

Accordingly, Applicants submit that the rejections of claims 272, 273, 280, 282-284, and 291 under 35 U.S.C. § 112, first paragraph for alleged lack of written description sufficient to show possession of the claimed invention are overcome.

The Rejections under 35 U.S.C. § 112, first paragraph (enablement)

Claims 272, 273, 280, 282-284, and 291 stand rejected under 35 U.S.C. § 112, first paragraph as allegedly failing to comply with the enablement requirement, the USPTO suggesting that the claims

contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Applicants traverse this rejection for at least the reason that Claims 272, 273, 280, 282-284, and 291 are directed to methods which recite the gene that encodes for a native sequence PR0224 polypeptide, and that particular sequences, SEQ ID NO: 1 and SEQ ID NO: 2, are disclosed in the application; that the methods recite mammals comprising a disruption of the gene that encodes for a native sequence PR0224 polypeptide, which sequences are provided; that the claimed methods require knock-out mammals with a phenotype comprising an eye abnormality, as disclosed in the application; and that methods for generating such knock-out mammals, and for measuring eye abnormalities, are taught in the application. Thus, Applicants submit that the teaching of the application is sufficient to enable one of ordinary skill in the art to practice the claimed invention without undue experimentation.

In particular, the USPTO suggests that the breadth of the invention encompasses a method comprising providing any non-human transgenic animal, and measuring any physiological characteristic of the non-human transgenic animal (USPTO's emphasis; pages 11-12 of the instant Office Action). However, Applicants submit that the USPTO's concerns are overcome by the disclosure of the application, the knowledge and skill of one of ordinary skill in the art, and in view of the present claim amendments.

Applicants note that the present claims are directed to methods comprising providing a non-human transgenic mammal, and that the disclosure describes methods applicable to mammals, including humans, mice and rats, and discloses results from humans and mice. Thus, Applicants submit that the claimed methods do not encompass a method comprising providing any non-human transgenic animal, as the claimed methods are limited to mammals. Accordingly, Applicants submit that the claims are not overbroad.

Applicants further note that the present claims are directed to methods comprising measuring a physiological characteristic of an eye of a non-human transgenic mammal, and that the disclosure describes methods and mesaurements of a physiological characteristic of an eye of a transgenic mammal (see, e.g., page 163, line 33 to page 164, line 20, and elsewhere in the application). Thus, Applicants submit that the claimed methods do not encompass a method comprising measuring any

physiological characteristic of the non-human transgenic animal, but instead are directed to particular kinds of physiological measurements, comprising physiological measurements of an eye of a transgenic mammal. Accordingly, Applicants submit that the claims are not overbroad.

The USPTO also discusses several scientific articles, and suggests that "the status of art indicates that generation of non-human transgenic animal is unpredictable." However, Applicants note that the results disclosed in the application, in view of the disclosure and of the skill and knowledge of one of ordinary skill in the art, provide a sound basis for the practice of the claimed methods without undue experimentation.

Much of the discussion on pages 12-13 of the instant Office Action is directed to scientific literature related to transgenic mice, embryonic stem cell methods, and is cited to suggest that the generation of a non-human transgenic animal is allegedly unpredictable. Applicants note that the present application, and, for example, the Clark, Montoliu, and Ristevski references cited by the USPTO, discuss methods for generating transgenic mammals which do not utilize embryonic stem cells, so that the concerns discussed by the USPTO regarding embryonic stem cell methods may not apply to all methods of generating transgenic mammals. Moreover, as discussed previously, the present application discloses the generation of non-human transgenic mice having a disruption in the gene that encoded for PRO184, and provides detailed methods and teaching regarding the generation and use of these mammals (see, e.g., page 162, line 18 to page 164, line 20). In particular, the present application not only discloses the methods that were used by the inventors to produce such mammals, but disclose methods for measuring physiological characteristics of an eye of such mammals, as well as presenting the results of such measurements on transgenic mice produced by these methods. Thus, Applicants submit that, despite the scientific literature cited to suggest that such methods might be unpredictable, Applicants provide sufficient teaching and experimental results as to teach one of skill in the art how to practice the claimed invention without undue experimentation. Even in view of the concerns raised by the USPTO, the teaching and experimental results provided in the application, in view of the skill and knowledge of one of ordinary skill in the art, is sufficient to enable the practice of the claimed invention without undue experimentation.

The USPTO stated that step (e) of claim 272 does not relate back (page 16 of the instant

Office Action); however, as amended, Applicants note that step (e) of claim 272 relates back to the phenotype (eye abnormality), and recites "whereby an agent which is determined to modulate an eye abnormality associated with a disruption of the gene that encodes for the native sequence PR0224 polypeptide is identified."

The USPTO is concerned that allegedly there may be no clear association between a phenotype of retinal abnormality (retinal degeneration) and a physiological characteristic of increased mean artery-to-vein (A/V) ratio (e.g., pages 15-16 of the instant Office Action, citing Upton *et al.*). However, Applicants note that Upton *et al.* did not investigate retinal abnormalities, but instead is directed to measurements of axonal projections in brainstem nuclei (superior colliculus and lateral geniculate) originating from the retinal ganglion cells in knock-out mice as compared to wild type mice. Thus, although axonal projections to the superior colliculus the lateral geniculate are clearly of importance to vision, it is not clear how the Upton *et al.* might relate to a phenotype of *eye abnormality*, nor to a physiological characteristic of increased mean artery-to-vein ratio. As Upton *et al.* do not discuss retinal abnormalities, it is unclear how Upton *et al.* relates to the present claimed invention.

Applicants submit that measurements of artery and vein dimensions or properties, in the retina, which differ between knock-out and wild type mammals, are by definition directed to *eye abnormalities*, as in such a case, the eyes of knock-out mammals differ from the eyes of wild-type mammals. Thus, Applicants believe the USPTO's concerns regarding the association between retinal abnormality and increased mean artery-to-vein ratio are overcome.

On pages 16-17 of the instant Office Action, the USPTO again suggests that allegedly "the phenotype of transgenic animal, including transgenic mouse, is unpredictable," citing Matthaei (page 16, lines 21-22 of the instant Office Action). However, even in view of the possible concerns raised by the USPTO, Applicants note that the present claimed invention is directed to methods which include an internal control, e.g., require comparison of knock-out and wild-type mammals, so that possibly "unpredictability" is believed not to be a concern. In addition, Applicants note that the present methods are directed to methods using knock-out mammals having an eye abnormality; thus, even if there were to be any "unpredictability" in the production of knock-out mammals, the methods

require knock-out mammals having the phenotype comprising an eye abnormality, and the methods are quite adequate and predictable for identifying an agent which modulates that phenotype. Acordingly, Applicants submit that the concerns regarding subjects discussed by Matthaei are overcome.

Accordingly, Applicants submit that the rejections of claims 272, 273, 280, 282-284, and 291 under 35 U.S.C. § 112, first paragraph for alleged lack of enablement are overcome.

CONCLUSION

Applicants believe that the present application is in *prima facie* condition for allowance. Thus, all claims are believed to be in form for allowance, and speedy notice of their allowance is respectfully requested.

Accordingly, reconsideration and allowance of all claims is respectfully requested. Should there be any further issues outstanding, the Examiner is invited to contact the undersigned attorney at the telephone number shown below.

Please charge any additional fees, including fees for additional extension of time, or credit overpayment to Deposit Account No. **50-2387** (referencing Attorney's **Docket No. (24126-286 (GNE-5201 R1))**.

Respectfully submitted,

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